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COMPLETE SPECIFICATION

Salts of Substituted Pyrrolidines and Compositions containing them

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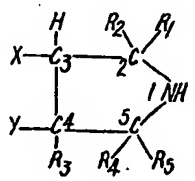
This invention is concerned with new pyrrolidine derivatives having useful pharmacological properties.

The new compounds according to the invention are non-toxic acid addition salts of compounds of the general formula:—



in which X is an aryl, furyl or thienyl group, Y is hydrogen, an aryl, furyl or thienyl group and R_1—R_5 which may be the same or different are hydrogen atoms or alkyl groups having from 1—4 carbon atoms.

By the term "non-toxic acid addition salts" we mean such salts, the anionic portions of which are non-toxic and compatible with the body.

The new salts according to the invention have valuable pharmacological properties, in particular an analeptic effect. The new salts further have a marked appetite-restraining effect and are thus useful for the treatment of conditions of depression and of obesity. In general a suitable single dose of the compounds is 5—50 mg, preferably 5—20 mg.

The salts according to the invention can be used also in combination with other substances, e.g. anti-histamines, barbituric acid derivatives and vitamins.

The free bases of the above formula are not suitable for therapeutic use since they are strongly alkaline and are thus incompatible with the body. The bases further have the disadvantage that under the influence of light and air they readily discolour, with the formation of undesirable by-products; these also mostly have an unpleasant odour. The free bases are mostly liquid, whilst the salts are crystalline.

Preferred salts according to the invention are the hydrochlorides, sulphates, hydrobromides, phosphates, lactates, citrates, tartrates, salicylates, acetates, formates, benzoates, succinates, ascorbates, gluconates and methanesulphonates of the bases of the stated formation, preferred bases being 3-phenyl-5-methyl-pyrrolidine and 3-phenyl-2,5-dimethyl pyrrolidine.

The toxicity of the new salts is low. Thus, on subcutaneous application, the lethal dose for the white mouse was 100 mg/kg e.g. for 3 - phenyl - 5 - methyl - pyrrolidine hydrochloride, and 250 mg/kg for 3-phenyl-2,5-dimethyl-pyrrolidine hydrochloride. These two last mentioned compounds are particularly preferred new compounds.

The new salts according to the invention can be prepared in any convenient manner. Preferably the salts are prepared from the purified parent base by reaction with the appropriate acid; the term "purified parent base" includes mixtures of otherwise pure stereoisomers where such exist. Thus it is generally preferable to prepare first a salt of the base with a strong mineral acid which is then purified by filtering a hot solution of the salt, making the filtrate alkaline to liber-

ate the free base and reacting this with the desired acid to yield the desired salt. Thus for example, purification of the crude base may be effected by dissolving the crude base in a strong mineral acid, heating the solution, filtering the hot solution to remove any solid impurities, if desired in the presence of a decolourising agent, e.g. active charcoal, making the filtrate alkaline, e.g. by addition of sodium hydroxide, and distilling off the free pure base which is then reacted with the desired acid to yield the desired salt. The pyrrolidine bases can be prepared by generally known methods.

The new salts according to the invention can also be useful for separating such salts of the pyrrolidine bases as exist in cis- and trans-forms, such separation being effected for example by fractional crystallisation. The cis- and trans-forms sometimes have slightly different pharmacological properties.

The invention further includes pharmaceutical preparations comprising the new compounds together with pharmaceutical carriers or diluents. Preferred preparations are those for oral administration, which may be solid e.g. tablets, capsules, dragees or pills, or liquid, e.g. syrups, elixirs or drops generally containing dispersing, sweetening, flavouring or buffering agents. Injectable preparations in a sterile parenterally acceptable liquid and suppositories may also be prepared.

For the better understanding of the invention the following examples are given only as illustration.

EXAMPLE 1.

200 g of distilled 3-phenyl-5-methyl-pyrrolidine ($B.pt._{14}$ 120—121° C.) are emulsified in 250 ml of water and 2 N HCl are added to acid reaction. The crystal paste, remaining behind after the evaporation of the solution, is washed once with 200 ml of ice-cold acetonitrile, the 3-phenyl-5-methyl-pyrrolidine hydrochloride being thus obtained almost pure. After recrystallising once from 250 ml of acetonitrile, the salt is analytical-grade.
Yield 90%, calculated on base used.
Melting point of the hydrochloride 123° C.

For the production of another salt from the hydrochloride, a concentrated aqueous solution thereof is made alkaline with 20—30% aqueous caustic soda and exhaustively extracted with ether, chloroform or benzene. From this base after distillation there can be produced any desired other salts of organic carboxylic acids or inorganic acids in usual manner.

EXAMPLE 2.

Isomer separation of 2,5-dimethyl-3-phenyl-pyrrolidine by fractional crystallisation of the salts.

300 g. of 2,5-dimethyl-3-phenyl-pyrrolidine (produced from benzalacetone and nitroethane by alkaline condensation at 80° C. and subsequent catalytic hydrogenation with Raney nickel in methanol at 80° C. and at 100 atmospheres gauge hydrogen pressure) which has a composition of about 50% α form, about 30% β form, 8—10 γ form and traces of δ form, are stirred into parts of 240 g of salicylic acid in 300 ml. of ethanol. A clear solution is formed with heat development from which 250 g. of pure salicylate crystallise out on cooling. The solid is filtered, washed with a little cold ethanol and finally with ample acetone. The mother liquor as well as the washing solvent are substantially concentrated and the oily residue is triturated with 75 ml of warm methanol. In this manner still more salicylate is obtained which is combined with the 250 g of crude salicylate. The salicylate now consists of about 60% of the β form, about 35% of the α form and traces of δ form. The melting point of this mixture is unsharp at 50—155° C.

The first precipitation of the salicylate can also take place in methanol instead of ethanol. In this case the crystallisation starts only hesitatingly, however, and requires about 24 hours to complete. The yield in salicylate only amounts to 160—180 g. The proportion of α form, however, is substantially less.

The so obtained crude salicylate is recrystallised three to four times from methanol until a melting point of 168—169° C. is reached. Besides the β form no other form of impurities of any kind must be traceable by gas-chromatography. The combined mother liquors from the recrystallisations are evaporated to dryness and the crystallised residue recrystallised from methanol in the same manner. Altogether about 85% of the β form, contained in the crude base, are thus obtained as pure salicylate. This can be converted in the usual manner into the free base and the hydrochloride produced therefrom. M.pt. 167° C. (from isopropanol).

From the combined last mother liquors as well as from the oily residue of the first precipitate, the α isomer can be isolated in pure form. For this purpose the mother liquors are evaporated to dryness, and the free base produced in usual manner. This is fractionally distilled in vacuo, and the fraction, b.pt. 115—125° C. 14 mm, collected. The colourless, water-clear base is suspended in about the double volume of water and concentrated hydrochloric acid added to acid reaction. This hydrochloride solution is evaporated in vacuo to dryness and the crystalline residue is recrystallised from acetonitrile to constant melting point. In this manner 75—80% of the α form, contained in the crude base, are obtained as the hydrochloride, M.pt. = 180—181° C.

From the mother liquors of the hydrochloride of the α form, the γ isomer can be isolated. It is more advantageous, however, to start for the production of the pure γ isomer from a crude base which, apart from impuri-

ties, consists almost exclusively of the γ form. This is obtained by condensing benzalacetone with nitroethane under alkaline conditions at low temperatures, followed by hydrogenation with platinum as catalyst in methanol at 50° C., and 20 atmospheres gauge hydrogen pressure. The conversion of the base into hydrochloride takes place as stated in Example 1. For removal of a small quantity of α and β form, the crude hydrochloride is boiled under reflux, alternately with acetone and with ethyl acetate, for one hour each time, and filtered by suction after cooling, until no more α and β form is traceable by gas chromatography. The product is recrystallised from acetonitrile. M.pt. = 139—141° C.

EXAMPLE 3.

A mixture of cis- and trans- 2-methyl-3-phenyl-pyrrolidine salicylate is extracted with boiling cyclohexane, only the one form dissolving. After recrystallisation, this has m.pt. 108—110° C. The residue of the extraction was recrystallised from isopropanol to constant melting point. M.pt. = 142—144° C.

The analysis of these two substances is identical for both steric forms of 2-methyl-3-phenyl-pyrrolidine salicylate.

EXAMPLE 4.

Corresponding to the working method according to Example 1, the following salts were produced:

a) 2,5 - dimethyl - 3 - phenyl - pyrrolidine hydrochloride, m.pt. = 139—141° C.

b) 2 - methyl - 3 - phenyl - pyrrolidine hydrochloride, m.pt. = 119—120° C.

c) mono - 2 - methyl - 3 - phenyl - pyrrolidine citrate. $1C_2H_5OH$ m.pt. 83—87° giving off alcohol of crystallisation.

d) mono - 2 - methyl - 3 - phenyl - pyrrolidine citrate. $1H_2O$, m.pt. = 60—62° C. (glassy melt).

e) 5 - methyl - 3 - phenyl - pyrrolidine acetate, m.pt. = 90° C.

f) 3 - phenyl - 5 - methyl - pyrrolidine sulphate (hygroscopic).

g) 2 - methyl - 3 - phenyl - pyrrolidine benzoate, m.pt. 105—106° C.

h) 2,2,5 - trimethyl - 3 - (α - furyl) - pyrrolidine hydrochloride, m.pt. = 202—204° C.

i) 5 - methyl - 3 - phenyl - pyrrolidine hydrobromide, m.pt. = 117—118° C.

j) 2,2,5 - trimethyl - 3 - phenyl - pyrrolidine hydrochloride (α form, free of β form) m.pt. = 225—227° C. (from isopropanol).

k) 3,4 - diphenyl - pyrrolidine hydrochloride, m.pt. = 188—191° C.

l) 3 - phenyl - 4 - methyl - pyrrolidine oxalate (α form) m.pt. = 87—90° C. (from isopropanol).

m) 3 - phenyl - 5 - ethyl - pyrrolidine hydrochloride (α form), m.pt. 97—99° C. (from ethyl acetate).

EXAMPLE 5.

2 - Ethyl - 5 - methyl - 3 - phenyl - pyrrolidine HCl(β form)

The β form of 2-ethyl-5-methyl-3-phenyl-pyrrolidine was obtained analogously to Example 2. The separation of the isomers by recrystallisation was carried out, however, with ethyl acetate instead of methanol. Melting point of the pure β salicylate 172—173° C. The hydrochloride was produced from this salicylate in usual manner. M.pt. = 229—231° C. (from acetonitrile).

EXAMPLE 6.

2 - Methyl - 3,4 - diphenyl - pyrrolidine hydrochloride, m.pt. = 188° C. α,β-Diphenyl-laevulinic acid nitrile, produced from α-phenyl-benzalacetone and acetonecyanhydrin is hydrogenated in methanol with Raney nickel at 70° C. and 100 atmospheres gauge pressure. The 2-methyl-3,4-diphenyl pyrrolidine boils at 122—123° C./0.01 mm.

This base is converted according to the process of Example 1 into 2-methyl-3,4-diphenyl pyrrolidine hydrochloride, m.p.t = 188° C.

Pharmaceutical Formulation

Example 7

Tablets

3-Phenyl-5-methyl-pyrrolidine hydrochloride	10.0 mg
Corn Starch	70.0 mg
Finely divided silica	2.5 mg
Soluble starch	2.0 mg
Magnesium stearate	0.5 mg
	85.0 mg

1 tablet of 85 mg contains 10 mg of 3-phenyl-5-methyl-pyrrolidine-hydrochloride.

Dragees

3-Phenyl-2,5-dimethyl-pyrrolidine hydrochloride	10.0 mg
Lactose	25.0 mg
Corn starch	22.0 mg
Soluble starch	1.7 mg
Finely divided silica	1.0 mg
Magnesium stearate	0.3 mg
	60.0 mg

Dragee mass 50 g, 1 Dragee of 110 mg. contains 10 mg of 3-phenyl-2,5-dimethyl-pyrrolidine hydrochloride.

Depot-tablets

3-Phenyl-5-methyl-pyrrolidine hydrochloride	20.0 mg
Fatty acid ester melting point above 50° C.	110.0 mg
Tablet filler	20.0 mg
Talc	9.0 mg
Magnesium stearate	1.0 mg
	160.0 mg

1 tablet contains 20 mg of 3-phenyl-5-methyl-pyrrolidine hydrochloride.

Gelatine capsules

3-Phenyl-2,5-dimethyl-pyrrolidine hydrochloride	10.0 g
Potato starch	15.0 g
Lactose	75.0 g
	100.0 g

The substances are carefully ground and mixed.

100 mg. of the mixture are in each case filled into one half of a gelatine capsule, and this is sealed with the second half of the capsule. 1 capsule contains 10 mg of 3-phenyl-2,5-dimethyl-pyrrolidine hydrochloride.

Syrup

3-Phenyl-5-methyl-pyrrolidine hydrochloride		0.20 g
Citric acid		0.19 g
Benzoic acid		0.09 g
Aroma essence		5.00 g
Alcohol		3.34 g
Sodium benzoate		0.09 g
Sugar		50.00 g
Water	ad	100.00 g

One dose = 1 tea spoon = 5 g = 10 mg of 3-phenyl-5-methyl-pyrrolidine hydrochloride.

Drops

3-Phenyl-2,5-dimethyl-pyrrolidine hydrochloride	1.00 g
Citric acid	1.00 g
Benzoic acid	0.45 g
Aroma-essence	5.00 g
Alcohol	16.70 g
Sodium benzoate	0.43 g
Sugar	20.00 g
Water	100.00 g

One dose = 10—20 — drops = 5 — 10 mg of 3-phenyl-2,5-dimethyl-pyrrolidine hydrochloride.

Ampoules

3-Phenyl-5-methyl-pyrrolidine hydrochloride		0.50 g
Sodium chloride		0.73 g
Aqua bidest	ad	100.00 g

100 ampoules at 1 ml; sterilised for 20 minutes at 110 — 120° C.

1 ampoule = 1 ml. = 5 mg of 3-phenyl-5-methyl-pyrrolidine hydrochloride.

Pills

3-Phenyl-2,5-dimethyl-pyrrolidine hydrochloride	1.0 g
Pill mass	20.0 g

1 pill = 0.1 g. = 5 mg. of 3-phenyl-2,5-dimethyl-pyrrolidine hydrochloride.

Combination with an antihistamine

Dragees:

3-Phenyl-5-methyl-pyrrolidine hydrochloride	20.0 mg
N-Phenyl-N-2-pyridyl-N^1,N^1-dimethylethylene diamine-HCl	50.0 mg
Lactose	20.0 mg
Corn starch	20.0 mg
Soluble starch	1.5 mg
Finely divided silica	1.2 mg
Magnesium stearate	0.3 mg
	113.0 mg

Dragee mass: 87 mg, 1 Dragee at 200 mg. contains 20 mg. of 3-phenyl-5-methyl-pyrrolidine hydrochloride.

Combination with a barbiturate derivative

Tablets

3-Phenyl-2,5-dimethyl-pyrrolidine hydrochloride	10.0 mg
5-Ethyl-5-isoamyl-barbituric acid	30.0 mg
Corn starch	37.5 mg
Finely divided silica	7.0 mg
Magnesium stearate	0.5 mg
	85.0 mg

1 tablet of 85 mg. contains 10 mg of 3-phenyl-2,5-dimethyl pyrrolidine hydrochloride.

Combination with Vitamins

Dragee core:

3-Phenyl-5-methyl-pyrrolidine hydrochloride	20.000 g
Vitamin B_1	6.000 g
Vitamin B_2	3.000 g
Vitamin B_6	1.000 g
Vitamin B_{12} (triturated with lactose 1:1000)	0.002 g
Calcium pantothenate	3.000 g
Nicotinamide	15.000 g
Ascorbic acid	55.000 g
Potato starch	80.000 g
Soluble starch	10.000 g
Lactose	81.190 g
Magnesium stearate	0.808 g
	275.000 g

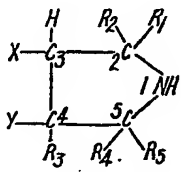
Dragee coating

Shellac	5.00 g
Sugar	114.00 g
Talc	80.96 g
Gum arabic	20.00 g
Titanium dioxide	5.00 g
White wax	0.04 g
	225.00 g

1 Dragee of 0.5 g. contains 20.0 mg of 3-phenyl-5-methyl-pyrrolidine hydrochloride.

WHAT WE CLAIM IS:—

1. Non toxic acid-addition salts (as herein defined) of pyrrolidine bases of the general formula:—



in which X is an aryl, furyl or thienyl group, Y is hydrogen or an aryl, furyl or thienyl group and R_1—R_5 which may be the same or different are hydrogen atoms or alkyl groups having from 1 to 4 carbon atoms.

2. The hydrochlorides, hydrobromides, sulphates, phosphates, lactates, citrates, tartrates, acetates, formates, benzoates, succinates, ascorbates, gluconates and methanesulphonates of pyrrolidine bases of the general formula specified in claim 1.

3. 3 - Phenyl - 5 - methyl - pyrrolidine hydrochloride.

4. 3 - Phenyl - 2,5 - dimethyl - pyrrolidine hydrochloride.

5. Pharmaceutical compositions comprising a compound as claimed in any of the preceding claims together with a pharmaceutical carrier or diluent.

6. Pharmaceutical compositions as claimed in claim 5 substantially as herein described.

7. A process for the preparation of salts as claimed in claim 1 in which a crude salt of a base of the stated formula with a strong mineral acid is purified by filtering a hot solution of the salt, making the filtrate alkaline to liberate the free base and reacting this with the desired acid to yield the desired salt.

8. A process for the preparation of salts as claimed in claim 1 substantially as described with reference to the examples.

9. A method of separation of a mixture of cis- and trans- isomers of a pyrrolidine base of the formula stated in claim 1 capable of existing in such forms which comprises fractionally crystallising salts as claimed in claim 1 of such mixture.

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